

Effect of Parathyroid Function After Thyroidectomy and Radioactive-Iodine Therapy for Thyroid Disease

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Abbreviations: TMNG: Toxic Multinodular Goiter; DTC: Differentiated Thyroid Cancer; RAI: Radioactive Iodine; PTH: Parathyroid Hormone; ICG: Indocyanine Green

ABSTRACT

Objective: Thyroidectomy and radioactive-iodine (RAI) treatment are two important methods for benign and malignant thyroid diseases. Thyroidectomy and RAI treatment may influence parathyroid gland function. This paper systematically reviewed the literatures on the effect of thyroidectomy and RAI on parathyroid gland function in patients with benign and malignant thyroid disease.

Subjective and Methods: We searched PubMed for English literatures by using terms of “thyroidectomy” or “radioactive iodine” and “hyperthyroidism” or “Graves’ disease” or “toxic multinodular goiter” or “toxic adenoma” or “differentiated thyroid carcinoma” and “parathyroid gland” or “calcium” or “parathyroid hormone” to review the effect of thyroidectomy and RAI on parathyroid gland function.

Result: Thyroidectomy may lead to hypocalcaemia and hypoparathyroidism both for benign thyroid disease and DTC. For benign thyroid disease, RAI treatment may cause increasing PTH in the short term and may induce parathyroid adenoma or hyperplasia in the long term. For DTC patients, parathyroid gland function may transiently decline after RAI treatment.

Conclusion: Thyroidectomy and RAI treatment may influence the parathyroid function in both benign and DTC patients. Thus, it is important to monitor PTH and blood calcium regularly in order to detect early abnormal parathyroid function for those patients.

Introduction

The thyroid gland is the largest endocrine gland in the human body. It secretes thyroid hormones that affect the metabolism. Hyperthyroidism including Graves’ disease (GD), toxic multinodular goiter (TMNG), toxic adenoma (TA) and differentiated thyroid cancer (DTC) are common thyroid diseases, for which thyroidectomy and radioactive iodine (RAI) treatment can be used. The parathyroid gland is an endocrine organ, which consists of 4 small glands located posteriorly to the thyroid in the middle aspect of the anterior neck and secretes parathyroid hormone (PTH), a polypeptide in response to low calcium levels detected in the blood. Low calcium can lead to circumoral or peripheral paresthesia, tetany, carpopedal spasm, laryngospasm, and ECG changes from long QT interval to VT arrest [1,2]. While high calcium can cause fatigue, polyuria, polydipsia, nephrolithiasis, peptic ulcer disease,

altered mental status, gait instability [3-5], myalgia, arthralgia, abdominal pain [4], rare submandibular gland atrophy and sialolithiasis, metastatic pulmonary calcification [6,7], sometimes even inducing acute kidney injury or acute pancreatitis [8-13], or being life-threatening [14,15].

The parathyroid gland is an adjacent organ of the thyroid. Theoretically, thyroidectomy and RAI may influence parathyroid function. The impairment of parathyroid glands and the thyroid function can produce some corresponding symptoms. It is necessary to focus on the effect of RAI and thyroidectomy treatment on parathyroid function. We searched PubMed for English language studies by using terms of “surgery” or “thyroidectomy” or “radioactive iodine” and “hyperthyroidism” or “Graves’ disease” or “toxic multinodular goiter” or “toxic adenoma” or “differentiated thyroid

carcinoma" and "parathyroid gland" or "calcium" or "parathyroid hormone (PTH)" to summarize the effect of thyroidectomy and RAI on parathyroid gland function in patients with above mentioned benign and malignant thyroid diseases.

Effect of Thyroidectomy on Parathyroid Function

Thyroidectomy meaning partial or complete removal of thyroid tissue is among the most frequently performed surgical procedures in general surgery for thyroid disease including differentiated thyroid carcinoma (DTC) and hyperthyroidism. Postoperative hypocalcemia due to hypoparathyroidism is the most common complication of thyroidectomy, with a reported incidence of 1.6% - 50% [16-18]. It is reported that post-operative hypocalcemia is frequently occurred in the first and second post-operative days. Permanent hypoparathyroidism after total thyroidectomy is associated with an increased risk of death [19]. Hypocalcemia after thyroidectomy for benign diseases, apart from more frequent symptoms of hypocalcemia in patients with Graves' disease, there were no differences in the overall frequency of biochemical hypocalcemia or decreasing PTH among benign and malignant thyroid diseases [20,21]. Generally thyroidectomy for hyperthyroidism rendered a patient to an euthyroid state faster than RAI [22]. After surgery for hyperthyroidism, young age, operative time, type of hospital, and parathyroid auto-transplantation were associated with early postoperative hypocalcemia [23].

Incidental parathyroidectomy with a reported incidence of 6.4% - 31.1%, was thought to be associated with postoperative hypocalcemia. Central neck dissection, total thyroidectomy, larger thyroid dimensions, extrathyroidal extension, tumor diameter more than 10mm, autoimmune thyroid disease, substernal goiter, females' gender were found to be significant risk factors of incidental parathyroidectomy [24-29]. Operative time and the amount of bleeding were not the risk factors [30]. However, in the study by Chew C, they found incidental parathyroidectomy did not contribute to significant changes in postoperative serum calcium levels [31]. The injury of parathyroid gland may compromise their blood supply and lead to hypoparathyroidism [32,33]. Intraoperative parathyroid imaging can be used to mitigate surgical hypoparathyroidism in the intraoperative setting [34]. A meta-analysis showed low level of intraoperative PTH and presence of parathyroid gland in the pathological specimen were also risk factors of post-surgical hypoparathyroidism [35].

Another meta-analysis [36] also showed that perioperative PTH, preoperative vitamin D and postoperative changes in calcium were biochemical predictors for post-thyroidectomy hypocalcemia and clinical predictors included female, re-operation for bleeding, heavier thyroid specimens, parathyroid auto transplantation. Parathyroid autografts not only increased the rate of postoperative hypocalcemia but may increase the chance of permanent hypoparathyroidism [37]. However, some studies revealed parathyroid auto transplantation is a vital tool to avoid or minimize the risk for

hypoparathyroidism following thyroidectomy [38,39]. The number of parathyroid glands remaining in situ was an important factor in prevention of permanent hypoparathyroidism [40]. A higher number of autos transplanted glands did not increase the chance of permanent hypoparathyroidism [39]. Thyroidectomy may cause hypocalcemia or hypoparathyroidism. Undiagnosed hypoparathyroidism can lead to multiple systemic sequelae such as chronic renal function impairment, reduced bone remodeling, increased psychiatric complaints and basal ganglia calcification [2,41]. It is important to monitor parathyroid gland function after thyroidectomy.

Parathyroid hormone assay twenty minutes after thyroidectomy is an accurate way for predicting clinically relevant hypocalcemia [42]. In the study by Filho E they found that serum intact PTH levels measured with 4 hour or on the first morning after surgery are predictors of postoperative hypocalcemia [43,44]. Some studies indicated that intact PTH level on the first day after total thyroidectomy is a very useful predictor of permanent hypoparathyroidism due to its high negative predictive value. Serum intact PTH levels above 5 pg/ml virtually exclude presence of permanent hypoparathyroidism [45,46]. Indocyanine green (ICG) angiography can predict the vascularization of the parathyroid gland and obviate the need for postoperative measurement of calcium and PTH [47]. The oral calcium and vitamin D supplements play an important role in order to avoid postoperative hypocalcemia and increase the likelihood of a safe and early discharge from the hospital [48]. Some factors associated with surgery [44] such as different anesthetic technique, site and procedure of surgery, duration of surgery, character of the patient can influence parathyroid function. A study reported that different anesthetic techniques can increase PTH levels from the reinduction to 3 minutes postinduction [49]. Some surgery of PTH excreting endocrine pancreatic neoplasm can decrease PTH and blood calcium levels [50,51]. Bariatric surgery may lead to the prevalence of secondary norm calcemic hyperparathyroidism, ranging from 17% - 70% [52,53]. The primary hyperparathyroidism patients who had parathyroid hyperplasia and osteoporosis may have higher incidence of postoperative hypocalcemia after parathyroidectomy [54].

Effect of RAI Treatment on Parathyroid Function for Benign Thyroid Disease

RAI treatment can be used in benign thyroid diseases including Graves' disease, toxic multinodular goiter or toxic adenoma. The therapeutic dose of RAI for benign diseases is lower than that for DTC. Since 1975 [55], the cases of subsequent development of hyperparathyroidism after RAI treatment has been reported. Colaco [56] summarized that 40 cases of RAI treatment patients eventually developed hyperparathyroidism (including parathyroid adenoma and hyperplasia) without finding any malignant tumor. The mean age of the patients at the time of RAI treatment was 58.9 ± 12.8 years and the mean latency period was 12.9 ± 8.8 years. The latent period was long. It could be the reason why a part of the

study concluded that radioactive contact had no obvious effect on parathyroid function [57-59]. Table 1 summarized the literatures reported on patients who developed hyperparathyroidism after RAI treatment. We can find that the latest hyperparathyroidism

occurred 30 years after RAI treatment, and most of them were female patients. Moreover, some studies showed that the latency period of benign lesions after radiation exposure was longer than that of malignant lesions [60-68].

Table 1: The literature reported on patients who developed hyperparathyroidism after RAI treatment.

Author	Cases	Sex	Disease	Age (years)	Latency (years)	Dose	Parathyroid Disease
Colaco, SM [56]	8	1M	Nodular goiter	38 - 54	Apr-35	N/A	Adenoma
	7F		Graves' disease				
Esselstyn [61]	4	F	Graves' disease	11-Aug	28-Jun	N/A	Adenoma/hyperplasia
KawamuraJ [62]	1	M	Graves' disease	24	12	12mci	Adenoma/hyperplasia
Bondeso [63]	7	F	Graves' disease	34 - 73	21-Mar	N/A	Hyperplasia/adenoma
Rosen [64]	4	M	Hyperthyroidism	20 - 57	30-Sep	N/A	Adenoma/hyperplasia
			Nodular goiter				
Cundiff [65]	1	F	Hyperthyroidism	67	6	N/A	Adenoma
Acar [66]	1	M	Nodular goiter	64	5	N/A	Adenoma
Netelenbos [67]	2	F	Nodular goiter	57 - 69	20-Nov	N/A	Hyperparathyroidism
Rasmuson [68]	11	M	Hyperthyroidism	22 - 75	19-Jan	6 - 30mCi	Adenoma

The specific mechanism of hyperparathyroidism after RAI treatment is still unclear, but the main risk factors may be related to age and treatment dose. Triggs and Williams [69] reported a high frequency of parathyroid adenomas in newborn rats after RAI treatment within 2 days of life. In addition, S Hanthi M [70] found that the older the patients were treated with RAI, the shorter the incubation time of developing hyperparathyroidism was. The parathyroid of older patients was more sensitive to RAI, which may be related to the instability of genes, thus leading to damage of apoptosis mechanism [71]. On the contrary, the younger the age of radiation exposure, the more likely it is to develop thyroid cancer earlier [72]. In the study by Piotr Szumowski [73], they treated benign thyroid diseases with absorbed dose of 140Gy, 180Gy and 240Gy according to different disease category, and found that PTH increased most significantly in patients with absorbed dose 240Gy within 6 months after RAI treatment. However, Hamilton TE [74] unmasked that the higher dose of exposure radiation may not increase the risk of hyperparathyroidism. Fjalling M studied 125 cases of hyperthyroidism patients after RAI treatment with an average followed-up 20 years [75]. It was found that there was no increase in the incidence of hyperparathyroidism, which may be a bias caused by relatively small number of cases.

There are few studies reported on the short-term effects of the parathyroid gland function after RAI treatment. In the study by Piotr Szumowski [73], they investigated the PTH changes in patients (including 220 cases of toxic goiter nodules, 20 cases of non-toxicity nodular goiter and 80 cases of Graves' disease) treated with RAI. The result showed statistically significant increases in above-normal PTH serum levels in all patients. The highest rise in serum level of PTH occurred in toxic goiter nodules patients and the

lowest in Graves' disease patients. Nevertheless, the blood calcium and blood phosphorus did not change significantly. The increase of PTH after radioactive iodine treatment may be caused by the inflammatory reaction caused by radiation. While blood calcium and phosphorus were maintained normal, which can be attributed to the mildly increased PTH whose action time was short and other regulatory mechanisms of calcium homeostasis could have been involved [76]. Ross DS [77], investigated PTH changes in 17 cases of hyperthyroidism patients after RAI treatment. The results showed that after therapy, patients quickly achieved hypothyroidism, whose PTH change was the most obvious (from 29 ± 15 to 75 ± 29 ng/ml). It is suggested that elevated PTH and blood calcium levels may be associated with iodine doses. More investigations are needed to elucidate the relationship between radiation dose and PTH or blood calcium change.

The treatment of benign thyroid diseases with RAI may cause increasing PTH with normal blood calcium in the early time, and development of adenoma and hyperplasia may occur in the long term. Three cases of hypoparathyroidism after RAI treatment has been reported [78-80]. There are case reports about patients appearing hypocalcemia after RAI treatment as well. Oksana Lazareva [81] reported 16-year-old young male patients with Graves' disease was given 15mCi RAI for treatment. After 11 weeks, he had paralysis, muscle spasms, fatigue and discomfort. Blood admission examination revealed reduced blood calcium and vitamin D, and highly increased PTH level. After in the process of oral calcium administration, blood calcium suddenly decreased. Eventually, it was considered as vitamin D deficiency and hungry bone syndrome (HBS)-a state of rapid calcium deposition into newly synthesized osteoid, resulting in rapid, profound, and prolonged hypocalcaemia

associated with hypophosphataemia and hypomagnesaemia [82]. Similarly, Kateryna Komarovskiy [83] also reported 12-year-old female children displayed hypocalcemia symptom after RAI treatment. It is worth noting that this patient also had vitamin D reduction. The specific mechanism for hypoparathyroidism after RAI treatment is not clear yet. To sum up, RAI treatment may cause hyper or hypo-parathyroidism for benign thyroid diseases. Blood calcium and PTH should be regularly monitored after treatment for these patients.

Effect of RAI Treatment on Parathyroid Function For DTC Patients

DTC is a common endocrine malignancy; the yearly incidence of DTC has nearly tripled from 4.9 per 100000 in 1975 to 14.3 per in 2009. One study predicted that PTC will become the third most common cancer in women by 2019 [84,85]. It is suggested that radiation exposure is associated with the development of thyroid carcinoma, especially the thyroid radiated directly by the irradiation dose (more than 50 - 100mGy). The smaller the contact's age and the greater the risk of thyroid cancer was [72]. This could be one of the reasons of the rising incidence of thyroid cancer. Other factors may include increased sensitivity of ultrasound scan, iodine intake, and compounds with carcinogenic potential, such as a large class of xenobiotics (flame retardants, pesticides, repellents, or thermal insulators) [86]. Currently, thyroid surgery, RAI treatment and TSH inhibition therapy have become the standard treatment regimen for DTC patients. Total thyroidectomy combined with RAI treatment will improve the overall treatment efficiency and enable patients to have higher quality of life [87].

RAI treatment following thyroidectomy is suggested for many DTC patients. The purpose of RAI treatment is to remove residual thyroid and small metastatic lesions, to facilitate postoperative follow-up and recurrence monitoring. High-dose RAI therapy is associated with decreased risk of recurrence in high-risk papillary thyroid cancer [88]. It is now accepted that the RAI treatment is very safe and the advantages of treating DTC with RAI outweigh the disadvantages [89]. Treatment with RAI can produce early and late complications. The common early complications include swelling and discomfort in the neck, xerostomia, dry eye, abnormalities of taste and smell, dysphagia, nausea, vomiting, bone marrow suppression [90], gonadal damage (hypospermia or temporary amenorrhea/oligomenorrhea), nasal dryness and obstruction, and nasolacrimal obstruction [91-96]. The late complications include permanent salivary gland dysfunction, leukemia and secondary malignancy, pulmonary fibrosis, fertility problems [97-102].

The parathyroid gland is an adjacent organ of the thyroid. Theoretically, RAI may influence parathyroid function. In the study by Aytekin Guven [103], 19 DTC patients after RAI therapy (therapeutic dose 100 - 150mCi) were measured PTH, blood calcium, phosphorus at the first, third, sixth, twelfth month. PTH

gradually decreased between the first and sixth month, but in the normal range, and restored baseline at twelfth month. Blood calcium level was similar to this trend without significant difference. Some patients appeared hypocalcemia without any clinical symptoms. Zhi-hua Zhao et al. [104] found there were still hypoparathyroidism happened after RAI treatment and the changes of PTH and blood calcium before and after the RAI treatment were not statistically significant. Generally, PTH reduced after RAI treatment for DTC, and a small number of patients could appear hypocalcemia. The underlying mechanism of diminished parathyroid function after RAI by a non-targeted effect of ionizing radiation called a "bystander effect" on the adjacent cells (RIBE) [103,105]. Gene expression changes may lead to RIBE occurrence [106]. There was one case reported that a patient developed hyperparathyroidism after RAI treatment for DTC. A 17-year-old male patient with thyroid papillary carcinoma underwent 2 times RAI treatment (total doses 263 mCi). Two years after RAI treatment, a parathyroid adenoma was detected by a neck ultrasound examination.

The specific risk factors that influence on the parathyroid gland function after RAI treatment for DTC are still needed to be further studied. Glazebrook G [107] found that age, sex, thyroid gland excision scope, operation method, iodine doses, neck radiation exposure, relative location between thyroid and parathyroid were not relevant risk factors of low parathyroid gland function. Aytekin Guven [103] found that age, gender, iodine dose had no impact on the PTH changes both before and after RAI therapy. Currently, the effect of RAI treatment on parathyroid gland function is not very clear yet. The studies mainly focused on the changes of PTH, blood calcium and blood phosphorus at different stages before and after the treatment of RAI. The sample sizes in these studies were small and the intervals of PTH and blood calcium measurement were different among different studies. No systematic study was published focusing on long-term (over one year) changes of PTH.

Conclusion

To sum up, thyroidectomy and RAI treatment may influence the parathyroid function in GD, TMNG, TA and DTC patients. Thyroidectomy may cause hypoparathyroidism and hypocalcaemia in benign and DTC patients. For benign thyroid disease, RAI treatment may cause increasing PTH in the short term and may induce parathyroid adenoma or hyperplasia in the long term. For DTC patients, parathyroid gland function may transiently decline after RAI treatment. It is important to monitor PTH and blood calcium regularly in order to detect early abnormal parathyroid function for those patients.

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Conflict of Interest

No conflict of interest.

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